GENERAL PATHOLOGY OF LYMPHOSARCOMA*

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WHEN all forms of primary tumors of lymph nodes are combined, the total incidence of this group of diseases becomes quite formidable. A search for statistical data brings to light the notable fact that there are no reliable data on this subject and also that in the present state of knowledge and the attitude of the medical public mind, there is no possibility of obtaining them. The United States Census of 1934 reports 1,512 deaths from pseudoleukemia and Hodgkin's disease, and 3,403 from the leukemias, while the majority of cases of fatal tumors of lymph nodes are classed under cancer of lymph nodes, from which it is impossible to determine how many were primary in the lymphatic system. It is well known that lymphatic diseases are more common in the Orient; and in Batavia, Java, the lymphosarcoma group ranks fourth on the list of deaths from cancer. From this state of affairs, one obtains support for the impression that lymphosarcoma, although a major medical problem, is a badly neglected field of observation, and that until some efforts are made to bring order into this chaos, beginning with nomenclature, little accurate information regarding the economic and social significance of this disease will be available. All that we know is that lymphosarcoma is a relatively common disease, nearly always fatal, of quite obscure etiology and pathology, generally difficult of diagnosis, and little influenced by treatment. All these facts were well known to Paltauf and Kundrat fifty years ago.

Etiological data being largely lacking, we are still compelled to rely upon morphology for the classification of tumors of lymph nodes. Applying this principle, three main structural varieties of these tumors are clearly distinguishable: lymphadenoma, lymphocytoma, and reticulum cell lymphosarcoma. Each of these varieties is associated with rather typical clinical characters and each is doubtless referable to specific etiological factors as yet undetermined. A simple scheme shows how specific structure goes with peculiar clinical course.

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Lymphadenoma:
Multiple giant follicular lymphadenoma—Brill's disease
Gastrointestinal pseudoleukemia
Lymphocytoma:
Systemic pseudoleukemia
Lymphocytic leukemia
Malignant disseminating lymphocytoma
Plasmacytoma
Solitary lymphoma
Reticulum Cell Lymphosarcoma: Large round cell lymphosarcoma affecting many regions and organs

The term lymphadenoma is appropriate because the lymph node is an organ and the lesion reproduces all the features of the organ in more or less orderly fashion but with varying grades of anaplasia and malignancy. In lymphocytoma the cell affected is the lymphocyte, while reticulum cells are passive. All grades of malignancy are observed. It is surprising how tardy has been the recognition of the specific features of reticulum cell lymphosarcoma. The most superficial comparison of the structure of a series of lymphatic tumors reveals the sharp distinctions between the small cell lymphocytic and the large reticulum cell sarcomas.

The early observers including Paltauf did not attempt fine distinctions between the different tumors of lymph nodes, but they fully recognized the two main varieties, small and large cell. Thirty years ago I began to point out to students the histogenesis of the two types of tumors of lymph nodes, and in 1913 in an article on endothelioma of lymph nodes, I discussed this subject in detail, supposing that it was so widely recognized among pathologists as to require little emphasis. Yet it was not until 1932 that an article by Roulet, proposing the term of reticulum cell lymphosarcoma, brought this term into general use. Ringertz of Stockholm has recently reviewed this history in detail.

A sketch of the main features of characteristic cases of the three varieties of lymphatic tumors may serve to emphasize their specific nature.

Lymphadenoma: Multiple giant follicular lymphadenoma is a systemic disease, usually widely generalized when first observed, affecting many or all groups of lymph nodes and the spleen, associated with rather moderate anemia, weakness, occasional mild pyrexia, running a progressive course, favorably affected by radiation, but recurring with increasing severity and generally proving fatal in five to ten years. The tumors

are not large and there is a limited scope of malignancy, but certain cases develop somewhat aggressive tendencies toward the terminal periods. Etiological factors are practically unknown. The structure shows a remarkable predominance and persistence of large, well-formed lymph follicles, with hyperplastic germ centers, with excess of lymphocytes of mainly normal type. In a few cases more diffuse growth may appear and the structure of diffuse lymphosarcoma may be produced.

Gastrointestinal pseudoleukemia is a term designating a very peculiar systemic disease affecting at times the entire gastrointestinal tract; producing myriads of small lymphomas in the mucosa from mouth to anus, without ulceration, and extending to many chains of lymph nodes and spleen; running a steadily progressive and rather active course with some fever, anemia, diarrhea, emaciation, peritonitis, and death within a few years or few months. The structure shows a remarkable tendency to be limited to the growth of many rather well-formed lymph follicles composed of normal or large lymphocytes and few reticulum cells, but lacking the diffuse growth of a malignant tumor or the ordinary type of systemic pseudoleukemia. Etiological factors are entirely unknown. I see nothing gained by merging these specific clinical entities with the general group of lymphosarcoma or pseudoleukemia, while the structural features are accurately indicated by the term lymphadenoma.

Lymphocytoma covers a wide field of clinical conditions and an equally varied morphology, determined mainly by the grade of malignancy and doubtless by the still undetermined etiology of most of its forms. At one end of the series stands the simple solitary lymphoma, a benign tumor composed of a diffuse growth of lymphocytes, occurring in many organs, often reaching a large size, and not recurring after operation or radiation. The average case of systemic chronic pseudoleukemia presents the structure of simple diffuse lymphocytoma. In many such cases a tuberculous etiology is well established. Lymphatic leukemia belongs in this group of lesions. The malignant forms of lymphocytoma present features which distinguish them from other types of lymphosarcoma, particularly from the reticulum cell sarcomas. Billroth's malignant lymphoma was the classic example of the older writers. This disease begins as a localized tumor of one node or chain, rapidly progressing, fusing the nodes, infiltrating the surrounding tissues and producing widespread metastases, generally aggravated by operation, now known to resist control by radiation or prone to recur, and

probably always fatal, with fever, anemia, and cachexia. The pathologist recognizes the terminal stages of malignant lymphocytoma by the widespread metastases, especially in serous membranes and in tissues not normally containing lymphatic tissue, and by the production of many, even myriads, of small lymphomas. The clinician may find little satisfaction in attempting to recognize distinctions between lymphatic disease before which he stands mainly a helpless observer. Intermediate grades of malignancy of lymphocytoma are found among the numerous cases of pseudoleukemia and lymphatic leukemia. That some of the very malignant forms represent terminal stages of the less malignant is illustrated in any broad clinical experience. On the other hand there are obvious differences between the most rapid lymphatic leukemia and the highly malignant lymphocytoma without leukemia. I recall a case of acute febrile lymphatic leukemia lasting eighteen days, with 600,000 leukocytes in the blood and widespread miliary lymphomas in the organs; but the lymphomas failed to affect the serous membranes, were never infiltrative, and exerted only mild pressure effects, whereas in the malignant tumor the lymphomas were universal, destructive, and produced aggressive tumors.

Reticulum Cell Sarcoma covers the main field of the lymphosarcomas and includes the great majority of the cases. The classical description of the older writers deserves repetition. The disease begins in a chain of nodes or in a localized area of a mucous membrane. All the nodes of the chain are affected from the first. The disease spreads by involving other chains of nodes but generally the whole new chain appears enlarged. The method of extension is obscure but probably involves both dissemination of the exciting agent and cell embolism. Isolated bulky metastases appear both in the lymphatic system and in other organs in which the new tumors arise in tissues entirely free from other signs of lymphatic irritation. Yet the primary focus is generally discernible at autopsy and appears to dominate the course of the disease. Hence early excision or radiation of the primary lesion has often controlled the disease. The clinical varieties and manifestations of reticulum cell sarcoma are extremely numerous, affecting every organ and tissue, obtruding themselves into every medical specialty, and at all ages.

Out of this complex clinical field, certain generalizations stand out prominently. There is the very notable healthy robust, overnourished appearance of the average subject of reticulum cell sarcoma, which is

sharply contrasted with most other forms of lymphatic diseases and especially with Hodgkin's disease. There is the tendency to localization, at least temporary, of the primary lesion. There is the tendency to limitation to the organ in which the disease arises, especially noted in lymphosarcoma of skin, spleen and bone marrow. There are rather specific cellular features detectable in lymphosarcoma of spleen, thymus, stomach, and some other organs, on which a localizing diagnosis may often be made. There is a notable frequency for the disease to terminate with streptococcus septicemia. A gloomy generalization relates to the highly lethal prognosis of this lesion in any form, so that one is compelled to regard with gravity the appearance of any spontaneous enlargement of a chain of lymph nodes, especially in an adult.

While the chief structural feature is simple enough, consisting in a diffuse growth of reticulum cells of varying degrees of anaplasia, there is a surprising variety in structural details which render the exact diagnosis and prognosis of lymphosarcoma one of the most difficult tests of the pathologist. It is seldom possible to predict whether the patient will live a few months or several years. Addicts to histological refinements point out certain peculiarities of structure, like Albertoni, who notes the lesser malignancy of tumors in which there are many large clear cells. The experienced pathologist contents himself with recognizing two main classes of structure in large cell lymphosarcoma, one being difficult to separate from a cellular infectious granuloma, while at the other extreme, one places the highly atypical diffusely growing process without any trace of granuloma. A fine intercellular argentophile reticulum is a characteristic structural feature.

In a serious effort to sharpen the diagnostic skill of pathologists, a Registry of Lymphatic Tumors was established at the Army Medical Museum some years ago. It makes progress slowly, chiefly because of the long period of observation required to complete the records, but now contains about 400 cases. It is a valuable mine of observation and opportunity for the student and deserves the hearty support of clinicians and pathologists, but it suffers from the general neglect visited upon the whole subject of lymphosarcoma and is seldom consulted. In this collection, the three classes of lymphatic tumors are fully illustrated and the diagnostic problems sharply emphasized. These problems consist chiefly in the distinctions between simple inflammatory and granulomatous inflammation, between tuberculosis and Hodgkin's disease, the

separation between inflammatory and neoplastic processes, and the recognition of grades of malignancy. All these problems constantly confront the pathologist and they are so difficult that one often wonders whether any adequate classification of lymphatic diseases is possible in the present state of knowledge.

The position of the leukemias in the scheme of lymphatic diseases is not easily determined, and is not adequately covered in the above groups which deal only with true primary tumors. Present knowledge indicates that the leukemic blood picture is a symptom arising under many different conditions and from a wide variety of etiological factors. Some of these processes are purely inflammatory and even transitory, others seem more or less autonomous, irreversible, and neoplastic, while in still others the underlying process is one of the many recognized varieties of malignant tumors of lymph nodes. On the ground that the leukemias are primary diseases of the bone marrow they might be excluded from the class of primary diseases of the lymphatic system. Yet it is unsafe to press this principle too far and for practical reasons the leukemias should be included in the general group of lymphomas. To cover the leukemias and certain other rarer forms of lymphatic disease, it is necessary to expand the classification and add to the three main classes of tumors certain subvarieties. Lymphatic leukemia falls with pseudoleukemia under lymphocytoma. Myelocytic leukemia is a specific process in which granular myelocytes are found in the hyperplastic nodes. Plasma cell leukemia, lymphomas, and lymphadenitis also stand out by themselves.

Endothelioma of lymph nodes: The doctrine that there is a specific group of primary tumors of lymph nodes, derived from the lining endothelium of cavernous and lymph sinuses, producing a structure resembling carcinoma, has been nearly wrecked by the discovery by Regaud and Schmincke of lymphoepithelioma. Probably the great majority of tumors recorded as endothelioma of lymph nodes were derived from the lining epithelium of mucous surfaces in which lymphatic tissue is abundant, as in the nasopharynx. Nevertheless the literature continues to supply rather frequent examples of tumors presenting the rather characteristic structure which the authors derive from lining endothelial cells. In many of these cases a clinical search or postmortem examination, which is stated to be thorough, fails to reveal any primary focus in the mucous membranes. I continue to see occasional cases submitted in which these conditions are asserted to exist and the structure

of the tumor and its clinical course are peculiar. In my own material I have not seen in recent years, any cases of this type in which a primary focus was positively excluded. While unable to deny that a primary endothelioma derived from sinus endothelium exists, I am inclined to think that cases of this type will diminish in frequency as observations become more precise and critical.

Etiology: An attempt to review the clinical data regarding the causation of lymphosarcoma is like looking into a fog at sea, and this impression is aggravated by inspection of current literature. Present day studies are wrestling with morphology, and there is little systematic effort to elucidate the problems of etiology. It is evident that lymphatic hyperplasia and neoplasia may be excited by a great variety of conditions which include every class of external irritant, supported by many contributing factors and favored by certain predisposing causes.

Subacute bacterial infection stands as one of the common excitants of lymphatic tumors, especially of skin and mucous membranes in man and lower animals. The pyogenic cocci, especially the group of streptococci, are most prominent in this relation, but many other microorganisms seem to be concerned in special cases. That subacute streptococcus infection is capable of producing lymphocytic and reticulum cell hyperplasia instead of polynuclear leukocytic exudate, was established long ago. In the skin, staphylococcus, ringworm, and many other common skin infections have been observed to precede lymphomatosis. A careful search for old or recent infections of skin and mucous membranes in cases of lymphosarcoma of these or deeper organs is rewarded with success in a large proportion of such cases and should always be undertaken. It is not an uncommon history that the patient suffered some months or years previously with a local infection accompanied by enlargement of regional nodes which subsided, but after a variable period the lymphatic enlargement returned in the form of lymphosarcoma. In a group of cases of deep lymphosarcoma, there is a history of typhoid fever, appendicitis, cholecystitis, salpingitis, or other local infection for which medical attention was required.

Most prominent among the established causes of lymphosarcoma are the infectious granulomas, including probably all of them, but especially tuberculosis and Hodgkin's disease. Tuberculosis is the chief causative agent in the entire group of lymphocytomas, but its relation to reticulum cell tumors is less definite. The transformation of a hyperplastic tubercu-

lous process into lymphocytoma has been observed many times, and the existence of a tuberculous process in such cases has probably often been overlooked. It has long been known that tuberculous infection with or without many tubercle bacilli may take the form of a nearly pure lymphocytic hyperplasia. In many cases of systemic pseudoleukemia, definite foci of tuberculosis may be found at autopsy.

The scope of morphology of Hodgkin's granuloma is so wide and its causative agent so uncertain that no definite statement may be made regarding its relation to lymphosarcoma. Hodgkin's granuloma affects reticulum cells more than lymphocytes, and one may assume that any lymphosarcomatous process arising on the basis of Hodgkin's disease would take the form of reticulum cell sarcoma. In typical cases of Hodgkin's disease, sarcomatous features may develop, involving the reticulum cells, but the process does not greatly resemble the typical reticulum cell sarcoma. That Hodgkin's disease ever takes the form of a true malignant neoplasm has never been proven, but it may be that certain cases of reticulum cell sarcoma arise on the basis of a Hodgkin's infection. Hodgkin's is the most typical of all the infectious granulomas, and the rather popular theory of its essential neoplastic character is without foundation.

An important relation of syphilis to any of the primary tumors of lymph nodes is not supported by very substantial data. Several less common infectious granulomas should probably receive more attention as possible causes of lymphomas. Micrococcus melitensis and venereal lymphogranuloma produce lesions closely resembling some of the atypical lymphomas, and subinfections by these agents may be concerned with some of the lymphosarcomas.

In the gastrointestinal tract, granulomas of undetermined origin affect stomach, bowel, appendix, and rectum, and produce lesions which greatly resemble in most respects the fully developed lymphosarcomas of these regions. Through such portals of entry, the deep thoracic and abdominal nodes are probably infected. In all cases of retroperitoneal lymphosarcoma, the gastrointestinal tract should be carefully searched for healed or small active lesions.

Constitutional factors seem to play a prominent part in the causation of the typical cases of reticulum cell sarcoma. This disease is remarkable for its predilection for robust, over-nourished, florid types of individuals who maintain their euphoria nearly to the terminal periods. Most of the

cases of Brill's disease also occur in such subjects. Veterinarians are quite familiar with the frequency of lymphosarcoma in cattle bred for the market, for hundreds of such animals are condemned every year for lymphomatosis. The nature of the predisposition established in such subjects is at present wholly obscure.

Experimental cancer research has brought out some peculiar etiological factors, the relation of which to human disease is quite uncertain. In mice, leukemia is produced by innoculation of cells and some strains are susceptible, others refractory. Leukemia has been produced experimentally in fowl by cell free extracts (Furth), by extracts of normal organs (Schridde), by benzol (Bungeler), and by radiation by radium or x-rays. Occasionally, leukemic or lymphomatous processes arise after the application of the cancerigenic cyclic compounds.

Criteria of Lymphatic Tumors: In the interpretation of lymphatic tumors, certain special criteria must be considered. Lymphatic tissue is present in nearly all tissues of the body and the total amount of this tissue is quite large. Lymph nodes are not fixed organs but come and go, varying in different species of animals, at different ages, in individuals, and in response to changing physiological conditions. The lymph node is the first barrier against infection which has passed the skin or mucous membrane, and the lymphocyte responds to irritation more readily than any other cell except the polynuclear leukocyte. The scope of reversible inflammatory hyperplasia is very wide and the existence of an irreversible neoplastic hyperplasia should not be assumed unless the autonomous characters are pronounced. There are physiological distinctions between systemic, thymic, and splenic cells and these often are traceable in tumors of these organs. There are free connections within the lymphatic system and with the blood vessels which render lymphatic tissue more or less mobile. This relation probably accounts for the tendency of lymphatic diseases to become systemic. It renders difficult the interpretation of metastases. There are indications that the extension of lymphatic tumors proceeds chiefly by cell embolism, but often by the development of new tumor cells by diffusion of the exciting agent. The possibility exists that growth stimulating cell products diffusing from the primary tumor focus may play a part in the remarkably wide and rapid extension of some lymphatic tumors. At times the whole lymphatic system seems to react as a whole.

There is a remarkable relation between lymphocyte and reticulum

cell most obvious in the follicles. Flemming's theory that the reticulum cells of the germ center are the mother cells of lymphocytes has been abandoned, for embryological and pathological data point strongly to the view that these two types of cells are distinct. In most pathological processes this distinction is rigidly maintained, but it cannot be denied that in some pathological conditions the two types of cells seem to grow together and the usual sharp distinctions are obliterated. The lymphocyte may reach considerable dimensions, while in some very active reticulum cell sarcomas, the cells may be rather small. Yet I have never seen any definite evidence of the existence of a mixed lymphocytic and reticulum cell sarcoma. The reticulum of reticulum cell sarcoma is usually prominent in this process while regularly absent in all stages of lymphocytoma. The growth of reticulum may account for the tendency to fibrosis observed in many reticulum cell tumors. Necrosis is notably lacking in both classes of lymphatic tumors. The failure of the lymphocyte to provide immunity against the infecting agent is a remarkable feature lacking explanation. This failure may be held responsible for the lethal character, however delayed it may be, of most lymphatic tumors and its granulomas. When enlarged lymph nodes appear anywhere in a subject after puberty, the outlook is always serious.

For many years pathologists have expressed the feeling that lymphosarcomas are not true tumors but require separate positions among pathological processes. They find that this process is so intimately connected with and dependent upon infection or extrinsic irritation, and presents so many features of an inflammatory process, that it may not be given a definite place among strictly autonomous neoplasms. This fact should be noted by workers with various so-called tumors among lower animals.

The foregoing sketch of the problems of lymphosarcoma impresses the critical observer mainly with the fragmentary character of our knowledge of this group of diseases. Every pathologist will admit that when faced with the simple question of diagnosis, he has as a rule to be content with a vague report on the general morphology of the process, but can offer little help regarding etiology, and must rely for prognosis on the generally fatal tendency of the disease. Regarding essential factors controlling the origin and progress of the disease, he must confess nearly complete ignorance. The clinician records the various incidents marking the course of the disease, but must acknowledge his inability

to alter the course except temporarily in the great majority of cases. His inquiry into etiological questions is handicapped by the absence of definite leads from the pathological side. The therapeutics of lymphosarcoma, although considerably encouraged by the occasional recoveries after radiation, is a gloomy chapter. The comparative frequency of these lymphatic diseases, and their occurrence in apparently healthy subjects of all ages, most of whom die in spite of all efforts, discourages optimistic attempts to improve the situation by clinical resources. Recognition of these outstanding facts has led to the establishment of at least one Foundation directed to the systematic study of one group of cases, the leukemias, while tragedies in many families have occasionally led to the granting of small sums to support of isolated workers. While the leukemias have been systematically pursued by experimental workers in several localities under the Tata Foundation, most of the work is undertaken by individuals who take up phases of the subject, pursue them for a time, and then become discouraged by the paucity of results, abandon the study, and wait for others to take up the burden and begin all over again.

Any comprehensive estimate of the scope of the problems of lymphosarcoma must lead to the conclusion that unless there is a systematic attack over a long period by a group of competent workers, under favorable conditions, with adequate material support, and including all phases of the subject, it is unreasonable to hope for any great progress. With this conviction in mind, the writer ventures to outline a program of systematic investigation which might be expected to bring some light on the fundamental questions involved, and possibly lead to some progress toward the prevention and control of this group of diseases. In offering the plan, it is realized that syndicated research has seldom been very successful in solving the major problems of medicine and that there are many practical difficulties in carrying out any such prolonged program even under the best auspices.

Plan of Systematic Investigation of Lymphosarcoma

Clinical medicine: The clinician may investigate the importance of heredity, the relation to status lymphaticus, and the possible relation of the endocrine organs. Metabolic studies are indicated as affecting the soil for bacterial growth. The history of the main organ affected should be searched for. The usual clinical data should be analyzed statistically.

The epidemiology of the disease should be considered.

Pathological anatomy: Full autopsies and study of all organs should be obtained. Chronic lesions in the affected organs should be noted, especially the oropharynx and gastrointestinal tract. The pathology of metastases should be more carefully investigated and interpreted. Radiographs of injected tissues might give important data. The relation between structure and prognosis should be determined in a large series.

Bacteriology: Bacterial studies of surgical and postmortem material should be pursued by appropriate methods. Little is known about the serology or immunology of the disease. The relation to bacterial antigens, and the effects of antigens made against whole tissues and tissue extracts and isolated bacteria invites attention. Bacterial mutation in the presence of lymphatic tissue is to be considered.

Experimental pathology: The reactions of lymphatic tissue to all the common pyogenic bacteria, infectious granulomas, and many chemical agents should be systematically determined. The reactions of lymph nodes to various tissue extracts, lipoids, and proteins of the tumors should be studied. The element of hypersensitization of lymphatic tissue may be considered. The action of known cancerigenic chemicals should be determined in lymph nodes. Do specific agents act selectively upon lymphocytes and reticulum cells?

Therapeutics: Radiological treatment should be standardized, and new modalities should be employed. The use of arsenicals in various combinations and as adjuvants to radiation is suggested by the work of Dustin. Antibacterial agents should be sought to control complications and terminal infections. The position of surgery should be determined.

Diagnosis: The standard of general diagnosis should be improved by the collection of a large series of fully observed cases as in the Lymphatic Tumor Registry. There might well be established a central bureau where very experienced observers would furnish diagnosis and prognosis. The general literature of the entire subject should be made available.

Such a project should be located in an institution or center where material is abundant, and where all the necessary scientific and clinical aids would be available or constantly occupied with one or more of the main problems. If such an organization were established, it would at least provide a center of reliable information and guidance, which is now lacking, and it would soon reveal the futility of the present efforts directed toward the solution of one of the major problems of medicine.